Remarks

The Interview

The Applicants, FemmePharma and the undersigned greatly appreciate the opportunity to meet with Examiners Kim and Fetterolf to discuss the present application on February 2, 2010, at U.S. Patent Office. During the interview, the FemmePharma representatives discussed the background of the company in developing women's products, the product in clinical trials (danazol formulated in a hydroalcoholic gel with a transdermal penetration enhancer that solubilizes the water-insoluble danazol so that it can penetrate the skin into the underlying breast tissue), the long standing need for the transdermal danazol product in treating breast disease without any systemic side effects, and the lack of any previous danazol transdermal product.

As discussed, the claims have been amended to limit the drug formulation to a hydroalcholic gel (page 8, line 11) comprising danazol and N-methyl-2-pyrrolidone or 2-pyrrolidone (page 9, lines 6 and 7), which both solublizes danazol and improves its delivery across the skin to the underlying breast tissue, so that the claims are commensurate in scope with the previously submitted declaration.

Information Disclosure Statement

Please note that information disclosure statements were filed on May 29, 2009, August 13, 2009, and January 27, 2010.

Amendments to the claims

Claims 1 and 10 have been amended to limit the drug to danazol and incorporate the limitations of claims 2 and 4, and specify that the carrier is a hydroalcoholic gel. The transdermal penetration enhancer is limited to N-methyl-2-pyrrolidone or 2-pyrrolidone. Support is found at page 9, lines 6 and 7. Claims 1 and 10 have also been amended to specify the formulation should deliver the drug across the stratum corneum to the underlying breast tissue. Support for this amendment can be found throughout the specification on page 7, lines 3 through 5, and page 7, line 27 through page 8, line 11. This is achieved in part by the penetration enhancer being able to solubilize the danazol. Support is found at page 6, lines 3 and 4, and page 7, line 26, to page 8, line 11.

Claim 10 has been further amended to specify that the method is for use in treatment of a disease or disorder of the breast treatable with danazol. Support can be found from page 1, lines 12 through page 3, line 15.

Claim 17 has been amended to limit the benign diseases of the breast to those treatable with danazol. Claims 2-5, 7, 8, 11, 12, 14, and 15 have been cancelled.

Rejection Under 35 U.S.C. § 102

Claims 1, 2, 4, 5, 7, and 8 were rejected under 35 U.S.C. § 102 as being anticipated by WO 00/72883 to Ragavan ("Ragavan-WO"). Applicants respectfully traverse this rejection to the extent is applied to the claims as amended.

Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc. v Monoclonal Antibodies Inc.*, 231 USPQ 81 (Fed. Cir. 1986); *Scripps Clinic & Research Found. v Genentech Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*:

"There must be *no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." (18 USPQ2d at 1010, emphasis added).

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation (*see Id.*).

WO 00/72883 to Ragavan ("Ragavan-WO")

Ragavan-WO is directed to pharmaceutical compositions for topical application to treat primarily skin conditions. The formulations of Ravagan-WO are directed primarily to the treatment of dermatological conditions, such as skin resurfacing procedures, sunburns, and inflammation due to toxic substances such as poison ivy (see pages 12 through 15) which can be treated using topical formulations without an enhancer. Ravagan-WO broadly discloses that "enhancers" such "oleic acid and other solvents" or the combination of a "diol and a cell-envelope disordering compound" may be added to the formulations.

Analysis

Claims 1 and 10, have been amended to specify the drug is a danazol, and clearly state that the formulation should be in an amount providing *regionally effective, not systemically effective* relief from benign diseases or disorders of the breast. Ragavan-WO discloses the use of topical and transdermal formulations to treat regional or systemic disorders. Ragavan-WO does not recognize that the drug formulation should produce locally effective levels only, **not systemically effective levels.** There is no mention of breast tissue and no examples of administering danazol, much less an effective dosage range for danazol. This is a critical aspect of the claimed method, as there are adverse side-effects associated with systemic delivery of danazol (see the specification, page3, lines 9 through 15).

Applicants have also amended the independent claims to specify that the formulation requires a hydroalcoholic gel and the specific penetration enhancers N-methyl-2-pyrrolidone or 2-pyrrolidone. Ravagan-WO does not discuss the use of N-methyl-2-pyrrolidone or 2-pyrrolidone.

For at least these reasons, the claims as amended are novel over Ravagan-WO.

Rejection Under 35 U.S.C. § 103

Claims 3 was rejected under 35 U.S.C. § 103(a) as obvious over WO 00/72883 ("Ravagan-WO"), and U.S. Patent No. 5,993,856 to Ragavan ("Ragavan 1"). Claim 3 has been cancelled. It is believed the rejection is now moot in view of the canceled claim. Claims 1 through 5, 7, and 8 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent NO.

5,993,856 to Ragavan ("Ragavan 1"). Applicants respectfully traverse this rejection to the extent is applied to the claims as amended.

The Legal Standard

The starting point for any such analysis must be the Supreme Court's decision in *KSR,* which refocuses the determination of whether a claimed invention is obvious back to the process the Court had defined in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). There, the Court had held that the obviousness determination should address four factors, all of which must be considered, though not in any prescribed order: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need. *Id.* The Court cautioned that the fact finder should be careful about reading the teachings of the invention at issue into the prior art, to avoid applying inappropriate hindsight, *ex post* reasoning. *Id.* at 36.

Analysis

(a) The scope of the prior art

U.S. Patent No. 5,993,856 to Ragavan ("Ragavan 1")

Ragavan 1 discloses formulations for topical or local delivery on reproductive organs to achieve relatively highly high blood levels in the regions to be treated in the substantial absence of systemic levels which might cause side effects. Ravagan 1 does not disclose the use of a hydroalcoholic carrier in combination with N-methyl-2-pyrrolidone or 2-pyrrolidone to

solubilize danazol and increase flux across the skin to the breast. The formulations of Ragavan 1 are intended for delivery across the mucosal membranes, which does not present the difficulty associated with delivery of the drug through the skin.

(b) Ascertaining differences between the prior art and the claims

As admitted the by the Examiner, Ravagan 1 does not illustrate a danazol formulation formulated with a hydroalcoholic carrier including a transdermal penetration enhancer, the formulation providing relief from disease or disorders of the breast and the property of the carrier *capable of delivering the drug to the breast tissue* and to promote delivery of the drug across the stratum corneum with low serum drug levels compared to the systemic administration of the drug (Office Action mailed September 30, 2009, bottom of page 5 to top of page 6).

The Examiner has suggested that one of ordinary skill in the art would recognize the disclosure of polyvinylpyrrolidone (PVP) as an excipient in Ravagan 1 as the penetration enhancer of the present claims. Without making any admissions, and solely to facilitate prosecution of the application, Applicants have further amended the claims to limit the transdermal penetration enhancer to N-methyl-2-pyrrolidone or 2-pyrrolidone. As discussed in the interview, and in the Declaration under C.F.R. 1.132 of Dr. Peter Mays, submitted with the Amendment and Response filed August 31, 2009, N-methyl-2-pyrrolidone or 2-pyrrolidone in combination with a hydroalcoholic gel acts as both a solubilizer for danazol ***and*** as a transdermal penetration enhancer, increasing flux across the skin. Most of the prior art discloses formulations where the danazol is in microparticulate form, not solubilized. The

microparticulate danazol will not penetrate the skin. This is obviated by the claimed formulation where the transdermal penetration enhancer is selected to solubilize the danazol. This produces results that are neither anticipated by, nor could have been predicted from, the prior art. In particular, the prior art only discloses the use of a material such as polyvinylpyrrolidone ("PVP") in combination with a hydrogel excipient.

As Dr. Mays states in paragraphs 18 and 19:

> *18. In the PEG ointment #1 15% pyrrolidone did not enhance danazol flux (0.004 μg/cm^2/hr), whereas in hydroalcoholic gel # 2 15% pyrrolidone in the presence of 47% alcohol enhanced the danazol flux rate (0.127 μg/cm^2/hr), a rate of flux twice that seen with oleyl alcohol alone (Exhibit 5, page 5, Table 2). This finding was unexpected.*
>
> *19. The combination of Danazol + Gel + Alcohol + PVP is not relevant to this application, as PVP, a known penetration enhancer, is a polymer which confers different physicochemical properties to the formulation than 2-pyrrolidone, which is a low molecular weight small molecule. Within the formulation of hydroalcoholic gel #2, the 2-pyrrolidone acts as both a solubilizer for danazol and a penetration enhancer.*

For at least these reasons, PVP is insufficient as a component of the danzol formulation of the present application.

(c) Secondary consideration of non-obviousness

The court has held that any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need, should also be considered.

As presented by Applicants during the interview, more than 26 million women in the United States suffer from fibrocystic breast disease. Traditional treatments, including oral danazol therapy, cause significant undesirable side effects. Only Applicants have developed a transdermal formulation that successfully delivers danazol across the breast skin to the underlying breast tissue, providing relief from benign diseases or disorders of the breast, without achieving systemically significant levels, or the associated side-effects. The claimed formulation overcomes the failure by others and provides a solution to the long standing but unmet need for treatment of breast pain in the substantial absence of side effects.

The declaration provides unexpected results. Applicants demonstrated that the claimed formulation including both a hydroalcoholic gel carrier and N-methyl-2-pyrrolidone or 2-pyrrolidone is more effective than other danazol formulations. As described in the declaration, a transvaginal formulation was ineffective in penetrating the skin (paragraphs 7 through 9). Although a transdermal formulation containing danazol, propylene glycol and oleyl alcohol did penetrate the skin, the flux was lower than when the formulation included a 2-pyrrolidone (0.055 $\mu g/cm^2/hr$) (Statement 13, and Exhibit 3, page 5, Table 2). The penetration enhancer 2-pyrrolidone was added to various formulations to improve the rate of flux, and formulations were tested for their ability to improve flux. 15% pyrrolidone did not enhance danazol flux (0.004 $\mu g/cm^2/hr$) in the PEG ointment (i.e., a non-alcoholic carrier). In contrast, 15% pyrrolidone in the presence of 47% alcohol enhanced the danazol flux rate (0.127 $\mu g/cm^2/hr$) of hydroalcoholic gel # 2, a rate of flux twice that seen with oleyl alcohol alone (Exhibit 5, page 5, Table 2). These

findings were unexpected. As discussed above, 2-pyrrolidone in combination with a hydroalcoholic gel acts as both a solubilizer for danazol *and* as a transdermal penetration enhancer, increasing flux across the skin. The data in the declaration is commensurate in scope with the claims as amended. The claims are now limited to a danazol formulation including a hydroalcoholic gel carrier and N-methyl-2-pyrrolidone or 2-pyrrolidone. The comparative data of the declaration describes the same formulation containing a hydroalcoholic gel carrier and 2-pyrrolidone.

Double Patenting Rejection

U.S. Patent No. 5,993,856 to Ragavan, et al. ("Ragavan 1")

Claims 1 through 5, 7 and 8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 through 15 and 31 through 33 of U.S. Patent No. 5,993,856 to Ragavan ("Ragavan 1"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

First, it should be noted that there is NO common ownership between this application and the '856 patent, which leads not to an obviousness type double patenting rejection, but a 103 rejection, as made and responded to above.

However, even if there were common ownership, independent claim 1 of Ragavan 1 defines micro- or nano-particulate drug formulation for local or regional topical administration of an effective amount to provide relief from symptoms associated with a disease or disorder in a

region in patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically.

Independent claim 31 defines a composition for treating endometriosis comprising danazol in a form promoting quick uptake into the blood stream when applied to the **mucosal** membranes of the female reproductive tract, wherein danazol is in a form delivering an effective amount to decrease the discomfort of endometriosis which is less than the effective amount when the drug is administered systemically.

For at least the reasons described above, the claims of Ravagan 1 do not teach the formulation of the instant application. As amended, claim 1 of the instant application recites danazol in a hydroalcoholic gel further comprising N-methyl-2-pyrrolidone or 2-pyrrolidone and wherein danazol is solubilized to enable delivery of danazol to the breast tissue. None of the claims of Ravagan 1 teach a hydroalcoholic gel carrier, or N-methyl-2-pyrrolidone or 2-pyrrolidone as components of the formulation. There is no mention of any of these elements, much less any disclosure leading one to combine them. Penetration enhancers that can be applied to the skin are quite different from those, if any, used to enhance uptake through the delicate mucosal tissues of the vagina or cervix! Therefore the claims of the present application are non-obvious over claims 1 through 15 and 31 through 33 of Ravagan 1.

U.S Patent No. 6,652,874 to Ragavan, et al. ("Ragavan 2")

Claims 1 through 5, 7, and 8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 through 4 and 17 of U.S.

Patent No. 6,652,874 to Ragavan ("Ragavan 2"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Independent claim 1 of Ravagan 2 defines a drug formulation comprising drug particles suitable for local or regional administration of an effective amount of the drug to provide relief from symptoms in a region in a patient in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically and wherein the drug is selected from the group consisting of anticancer drugs, cytotherapeutic drugs, anti-proliferative drugs, and antiviral drugs.

The same comments and analysis apply as above. The claims of Ravagan 2 do not teach nor make obvious the combination of a hydroalcoholic gel with N-methyl-2-pyrrolidone or 2-pyrrolidone containing an appropriate dosage of danazol for application to breast tissue for treatment of breast disease or disorders. It is the *combination* of the hydroalcoholic gel and N-methyl-2-pyrrolidone or 2-pyrrolidone that solublizes danazol and enhances flux of the drug through the skin of the breast and the dosage that are critical. One of skill in the art would not have recognized the need for this combination of components based on the claims of Ragavan 2. Therefore the claims of the present application are non-obvious over claims 1-4 and 17 of Ravagan 2.

U.S. Patent No. 6,416,778 to Ragavan, et al. ("Ragavan 3")

Claims 1 through 5, 7, and 8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 through 3 and 12 of U.S.

Patent No. 6,416,778 to Ragavan ("Ragavan 3") Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Independent claim 1 of Ravagan 3 defines a drug formulation comprising drug particles suitable for regional administration of an effective amount to provide relief from symptoms of a disease or disorder selected from the group consisting of endometriosis, endometrial bacterial infections, cancer, and endocrine conditions in a region in patients in need thereof, wherein the region is selected from the group consisting of the *uterus, fallopian tubes, peritoneal space, pelvic cul-de-sac, ovaries, and urinogenital tract*, wherein the effective amount is a dosage which results in low serum drug levels and reduced side effects as compared to systemic administration of the drug, and wherein the formulation is in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam.

Independent claim 12 defines a composition for treating endometriosis comprising particulate danazol in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug, when applied to the *mucosal membranes* of the female reproductive tract, wherein the carrier is selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam wherein the dosage of the danazol is effective to

reduce the symptoms of endometriosis without causing blood levels of danazol achieved with systemic administration of the danazol.

The same comments and analysis apply as above. The claims of Ravagan 3 do not disclose nor make obvious the combination of a hydroalcoholic gel with N-methyl-2-pyrrolidone or 2-pyrrolidone which is needed to both solublize and deliver the drug across the skin to the breast tissue, nor the dosage for treatment of breast disease or disorders. One of skill in the art would not have recognized the need for this combination of components based on the claims of Ragavan 3. Therefore the claims of the present application are non-obvious over claims 1-4 and 17 of Ravagan 3.

Withdrawal of the nonstatutory double patenting rejections is respectfully solicited.

Rejoinder and allowance of all claims 1, 10, 17, and 19 is respectfully solicited.

Respectfully submitted,

/Patrea L. Pabst/
Patrea L. Pabst
Reg. No. 31,284

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PABST PATENT GROUP LLP
1545 Peachtree Street, NE
Suite 320
Atlanta, Georgia 30309
(404) 879-2151
(404) 879-2160 (Facsimile)